The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: COR103561
Title: A Randomized, Double-Blind, Multi-Center Study Comparing the Effects of Carvedilol Phosphate Modified Release Formulation (COREG-MR) with Metoprolol Succinate (Toprol-XL) on the Lipid Profile in Normolipidemic, or Mildly Dyslipidemic Hypertensive Patients
Rationale: Hypertension and dyslipidemia are two of several modifiable risk factors for cardiovascular morbidity and mortality. The co-existence of dyslipidemia and hypertension increases the risk of cardiovascular disease more than the sum of the risks associated with each factor occurring alone . Beta-1 selective beta blockers while effective antihypertensive agents, are generally perceived to worsen dyslipidemia as well as to increase insulin resistance in hypertensive subjects. Beta blockers without adverse carbohydrate and lipid metabolism effects would provide a significant improvement in long term therapy of the high risk hypertensive subject.
Phase: IIIb
Study Period: 30 Dec 2005 -11 Dec 2007
Study Design: This was a randomized, double-blind, double dummy parallel group study to compare the effects of Coreg CR (carvedilol phosphate extended release capsules) to metoprolol succinate (Toprol XL) on the lipid profile of patients with hypertension and with normal lipids or mild dyslipidemia.
Centers: Subjects were enrolled at 97 centers in the US, 14 centers in Canada and 2 centers in Puerto Rico
Indication: Hypertension
Treatment: Subjects were randomized 1:1 (stratified by gender) to either Coreg CR 20 mg QD (dose level 1; DL1) or Toprol XL 50 mg QD (dose level 1; DL1) treatment. Following randomization, subjects returned for weekly Uptitration visits and were uptitrated on blinded study medication of either Coreg CR 40 mg to 80 mg or Toprol XL 100 mg to 200 mg until target blood pressure was maintained for 1 week (2 consecutive visits) or the subject had been on the highest dose of blinded study medication (DL3) for one week. Target blood pressure was defined as a systolic blood pressure of <140 mmHg and diastolic blood pressure of < 90 mmHg. Those subjects who did not achieve target blood pressure after receiving DL 3 study medication for one week also entered the Maintenance phase and returned for weekly visits during which adjunct medications were added to further reduce blood pressure to target. Adjunct medications were addition of 5 mg amlodipine which could be increased to 10 mg followed by addition of 12.5 mg of HCTZ which could be increased to 25 mg. Subjects were maintained on therapy for 24 weeks following which they entered the downtitration phase for 2 weeks.
Objectives: The primary objective of this study was to determine if the effect of Coreg CR on the lipid profile, as measured by the difference in the mean percent change from baseline in HDL-C or triglycerides was superior to the effect of metoprolol succinate (Toprol XL) in hypertensive subjects with normal lipids or mild dyslipidemia.
Primary Outcome/Efficacy Variable: The two coprimary efficacy endpoints were 1) change from Baseline to month 6 (LOCF) in triglycerides, and 2) change from Baseline to month 6 (LOCF) in HDL-C.
Secondary Outcome/Efficacy Variable(s): Secondary objectives were: to fully characterize within treatment group comparisons in HDL-C relative to initiation of therapy, from baseline to Month 6 (LOCF), to fully characterize within treatment group comparisons in triglycerides relative to initiation of therapy, from baseline to Month 6 (LOCF), to determine and compare the effects of Coreg CR and Toprol XL on additional measures of the lipid profile [total serum cholesterol, LDL-C levels, non-HDL-C (LDL+VLDL), HDL-C subfractions (HDL2-C, HDL3-C), LDL subparticles, atherogenic remnant lipids (IDL+VLDL), apolipoprotein-A1, apolipoprotein-B], glycemic parameters [fasting blood glucose, HbA1c, fasting insulin, c-peptide, insulin sensitivity (HOMA-%S)] and markers of inflammation (hs-CRP and LpPLA2 activity), to compare the percentage of subjects in each treatment group who must have withdrawn from the study due to worsening lipid parameters, to compare between treatment groups, the mean change from baseline to Month 6 (LOCF) in blood pressure (systolic and diastolic) and heart rate, to summarize the percentage of subjects in each treatment group requiring add-on therapy to reach target blood pressure at any time during the study, to evaluate clinical safety and tolerability within each treatment group using adverse experiences, laboratory evaluations, vital sign changes, and withdrawal rates, and to assess the occurrence of new onset diabetes mellitus (based on investigator assessment) in each treatment group at the end of the maintenance treatment (Month 6 LOCF).
Statistical Methods: The following analysis populations were defined:

Study No.: COR103561

Title: A Randomized, Double-Blind, Multi-Center Study Comparing the Effects of Carvedilol Phosphate Modified Release Formulation (COREG-MR) with Metoprolol Succinate (Toprol-XL) on the Lipid Profile in Normolipidemic, or Mildly Dyslipidemic Hypertensive Patients

•All Randomized: All subjects who were randomized to receive study medication, regardless of whether they took a dose.
•Intent to Treat Safety (ITTS): All randomized subjects who received at least one dose of study medication. All safety data were summarized by this population.
•Intent to Treat Efficacy (ITTE): All randomized subjects with efficacy (vital signs) data after a minimum of 2 weeks on treatment.

Continuous efficacy variables were analyzed by parametric analysis of covariance (ANCOVA) model adjusting for treatment, gender, region, and corresponding baseline efficacy variable. The data suggest that the normality assumptions of the above parametric analyses were violated for the co-primary endpoints and relevant secondary endpoints. A log transformation of the data was used for the HDL-C co-primary endpoint analysis. Due to outliers in triglycerides, normality assumptions were not met for the log transformed analysis. Therefore, a nonparametric analysis equivalent to the above ANCOVA model was used for treatment comparisons for the triglyceride co-primary endpoint. Logistic regression models were utilized in the analysis of binary efficacy variables. Missing values on therapy were estimated by the last (on therapy) observation available. For the co-primary analyses only, the treatment-by-baseline, treatment-by-gender, and treatment-by-center interactions were investigated individually but were not included in the model where main treatment effects were tested and compared.
Centers were sparsely populated and could not be used in the analyses; region was used for all analyses instead
All safety data were presented by appropriate statistical summaries. Efficacy Analyses: The co-primary analyses performed at the 0.025 significance level. All secondary statistical analyses performed at the 0.05 significance level. Tests for interaction were tested at the 0.10 significance level.

Study Population: For the comparison of mean percentage change from baseline in HDL-C at month 6 between Coreg CR and Toprol XL, 205 subjects per treatment group were required to provide 90% power to detect a difference of 5%. This assumed a two-sided test at a significance level of 0.025 and a common standard deviation of percent change from baseline in HDL-C of 14.35%. A sample size of 109 subjects in each of the two treatment groups were required to provide 90% power to detect a greater than or equal to 15% mean percentage change from baseline (- 0.1625 on log scale) for triglycerides in the Coreg CR group relative to the Toprol XL group. This assumed a two-sided test at a significance level of 0.025 and a standard deviation of change from baseline in triglycerides of 0.34 on the log scale. To achieve adequate power for both co-primary parameters, 205 evaluable subjects were required per treatment group (410 total subjects). To allow for an estimated screen failure rate of 50% and an estimated 20% withdrawal rate prior to Maintenance month 2 visit, it was assumed that approximately 1028 subjects needed be screened, from which approximately 514 subjects were expected to be randomized to yield 410 evaluable subjects.

	Toprol XL (N=278)	**Coreg CR (N=290)**	**Total (N=568)**
Randomized N	278	290	568
Completed n (%)	190 (68%)	221 (76%)	411 (72%)
Prematurely Withdrawn n (%)	88 (32%)	69 (24%)	157 (28%)
Primary reason for withdrawal			
Adverse Event	19 (7%)	21 (7%)	40 (7%)
Lost to follow-up	25 (9%)	7 (2%)	32 (6%)
Protocol Violation	18 (6%)	14 (5%)	32 (6%)
Subject decided to withdraw from study	19 (7%)	16 (6%)	35 (6%)
Sponsor terminated study	0	0	0
Non-compliance	1 (<1%)	3 (1%)	4 (<1%)
Insufficient therapeutic effect	4 (1%)	6 (2%)	10 (2%)
Worsening serum lipid levels	2 (<1%)	0	2 (<1%)
Other	0	2 (<1%)	2 (<1%)

Demographics and selected clinical characteristics at Baseline:

Study No.: COR103561				
Title: A Randomized, Double-Blind, Multi-Center Study Comparing the Effects of Carvedilol Phosphate Modified Release Formulation (COREG-MR) with Metoprolol Succinate (Toprol-XL) on the Lipid Profile in Normolipidemic, or Mildly Dyslipidemic Hypertensive Patients				
		Coreg CR (N=290)	**Toprol XL (N=278)**	**Total (N=568)**
Age (y)	Mean	51.7	52.2	52.0
	Min.	22	26	22
	Max.	79	80	80
Age Group	< 65 years	260 (90%)	244 (88%)	504 (89%)
	>= 65 years	30 (10%)	34 (12%)	64 (11%)
Sex	Female	137 (47%)	133 (48%)	270 (48%)
	Male	153 (53%)	145 (52%)	298 (52%)
Ethnicity	Hispanic/Latino	43 (15%)	45 (16%)	88 (15%)
	Not Hispanic/Latino	247 (85%)	233 (84%)	480 (85%)
Race group	Black	24 (8%)	28 (10%)	52 (9%)
	White/Caucasian	239 (82%)	226 (81%)	465 (82%)
	Other	27 (9%)	24 (9%)	51 (9%)
Baseline Sitting DBP (mmHg)	n[1]	290	277	567
	Mean (SD)	94.2 (6.03)	93.7 (6.46)	93.9 (6.24)
Baseline Sitting SBP (mmHg)	n[1]	290	277	567
	Mean (SD)	148.0 (9.95)	147.9 (9.98)	147.9 (9.95)
Baseline Heart Rate (beats/minute)	n[1]	288	276	564
	Mean (SD)	72.1 (8.45)	72.7 (8.90)	72.4 (8.67)
Body Mass Index (kg/m^2)	n[1]	283	274	557
	Mean (SD)	33.02 (6.888)	32.42 (6.180)	32.73 (6.550)
Baseline HDL-C (mg/dL)	n[1]	290	278	568
	Mean (SD)	45.9 (12.97)	45.0 (10.87)	45.4 (11.98)
Baseline Triglycerides (mg/dL)	n[1]	290	278	568
	Mean (SD)	189.5 (86.87)	190.4 (105.52)	190.0 (96.36)
Baseline Cholesterol (mg/dL)	n[1]	290	278	568
	Mean (SD)	207.5 (35.53)	205.8 (31.13)	206.7 (33.43)
Baseline LDL (mg/dL)	n[1]	267	255	522
	Mean (SD)	126.5 (31.20)	125.9 (27.06)	126.2 (29.22)
Risk Factor	n[1]	290	278	568
	0-1	108 (37%)	85 (31%)	193 (34%)
	>=2	182 (63%)	193 (69%)	375 (66%)
Framingham 10-year risk status	n[1]	290	278	568
	<10%	119 (41%)	119 (43%)	238 (42%)
	10-20%	62 (21%)	73 (26%)	135 (24%)
	>20%	1 (<1%)	2 (<1%)	3 (<1%)
	Not Calculated	108 (37%)	84 (30%)	192 (34%)
1. Subjects with a baseline value				
Primary Efficacy Results: Summaries of the changes from baseline and model adjusted changes for the coprimary efficacy endpoints are presented below.				

	Extended-Release Carvedilol (N=280)				Extended-Release Metoprolol (N=269)				Treatment Difference[3]	
Parameter (mg/dL)	**N [1]**	**BL**	**MM6**	**% Change from BL (95% CI) p-value[2]**	**N [1]**	**BL**	**MM 6**	**% Change from BL (95% CI) p-value[2]**	**% Change (97.5% CI)**	**P-value**
Triglycerides	235	167.26	169.03	2.65 (-2.40, 7.68) 0.3085	206	169.91	188.50	10.39 (5.17, 16.00) <0.0001	-8.026 (-15.35, -0.67)	0.0141
HDL-C	235	44.2	42.1	-4.4 (-6.2, -2.6) <0.0001	206	43.2	41.1	-5.1 (-7.0, -3.2) <0.0001	0.7 (-2.4, 3.9)	0.6068

1. Number of subjects with a value at baseline (BL) and Maintenance Month 6 (MM6)
2. p-value is for within-treatment difference between baseline and MM6
3. Treatment Difference for triglycerides is based on non-parametric ANCOVA and for HDL-C on ANCOVA using log transformation.

BL and MM6 values are medians for triglycerides and geometric means for HDL-C.

Secondary Outcome Variables:

Secondary objectives were: to fully characterize within treatment group comparisons in HDL-C relative to initiation of therapy, from baseline to Month 6 (LOCF), to fully characterize within treatment group comparisons in triglycerides relative to initiation of therapy, from baseline to Month 6 (LOCF), to determine and compare the effects of Coreg CR and Toprol XL on additional measures of the lipid profile [total serum cholesterol, LDL-C levels, non-HDL-C (LDL+VLDL), HDL-C subfractions (HDL2-C, HDL3-C), LDL subparticles, atherogenic remnant lipids (IDL+VLDL), apolipoprotein-A1, apolipoprotein-B], glycemic parameters [fasting blood glucose, HbA1c, fasting insulin, c-peptide, insulin sensitivity (HOMA-%S)] and markers of inflammation (hs-CRP and LpPLA2 activity), to compare the percentage of subjects in each treatment group who must have withdrawn from the study due to worsening lipid parameters, to compare between treatment groups, the mean change from baseline to Month 6 (LOCF) in blood pressure (systolic and diastolic) and heart rate, to summarize the percentage of subjects in each treatment group requiring add-on therapy to reach target blood pressure at any time during the study, to evaluate clinical safety and tolerability within each treatment group using adverse experiences, laboratory evaluations, vital sign changes, and withdrawal rates, and to assess the occurrence of new onset diabetes mellitus (based on investigator assessment) in each treatment group at the end of the maintenance treatment (Month 6 LOCF).

	Toprol XL (N=269) GM%* (95% CI)	**Coreg CR (N=280) GM%* (95% CI)**	**P-Value Treatment Difference**
Lipid Profile (mg/dL)			
Total serum cholesterol	-0.64% (-2.32, 1.08)	0.04% (-1.56, 1.66)	NS
LDL-C levels	-1.65% (-4.13, 0.90)	-1.09% (-3.43, 1.31)	NS
non HDL-C (LDL+ VLDL)	0.47% (-1.55, 2.54)	0.86% (-1.05, 2.79)	NS
HDL2-C	-6.79% (-11.30, -2.06)	-1.45% (-5.93, 3.25)	NS
HDL3-C	-3.50% (-5.40, -1.57)	-4.11% (-5.88, -2.31)	NS
LDL-Subparticles	-1.42% (-2.62, -0.22)	0.10% (-1.01, 1.23)	0.0634
Atherogenic remnant lipids (IDL+VLDL) (mg/dL)	5.81% (0.28, 11.64)	2.05% (-3.05, 7.42)	NS
Apo-A1 (g/L)	-3.45% (-5.38, -1.49)	-1.87% (-3.71, 0.01)	NS
Apo-B (g/L)	0.89% (-1.09, 2.91)	-1.04% (-2.87, 0.82)	NS

Glycemic Parameters			
Fasting insulin (IU/mL)	1.35 (-0.27, 2.96)	-1.21 (-2.71, 0.29)	.0213
c-Peptide (ng/mL)	0.20 (0.02, 0.39)	-0.23 (-0.40, -0.05)	.0007
HOMA-%S	-4.24% (-9.62, 1.46)	1.48% (-3.85, 7.11)	NS
FPG (mg/dl)	1.18 (-0.80, 3.17)	0.96 (-0.90, 2.82)	NS
HbA1c	0.01 (-0.04, 0.06)	0.04 (-0.01, 0.08)	-0.03 (-0.09, 0.04)
Vital Signs (mean ± SE)			
SBP (mmHg)	-17.47 (-18.82, -16.12)	-16.80 (-18.07, -15.53)	NS
DBP (mmHg)	-11.48 (-12.40, -10.57)	-10.89 (-11.75, -10.02)	NS
Heart Rate (beats/min)	-6.15 (-7.17, -5.12)	-5.85 (-6.82, -4.88)	NS
Other endpoints			
LpPLA2 activity (mcmol/min/L	-1.86% (-3.54, -0.15)	-2.32% (-3.86, -0.75)	NS
hs-CRP	2.30% (-7.61, 13.26)	0.22% (-8.92, 10.27)	NS
Weight	1.01 (0.46, 1.56)	0.73 (0.17, 1.30)	0.28 (-0.51, 1.06)

* 1. GM = Geometric Mean

Safety Results: An on-therapy AE was defined as an AE which occurred during the up-titration, maintenance, or down-titration phase, within 3 days post last dose. The safety population included all randomized subjects who received at least one dose of study drug. A summary of all on-therapy AEs, overall AEs by relation, overall AEs by intensity, SAEs, AEs leading to withdrawal and the most frequent on-therapy AEs are summarized below. Treatment emergent AEs occurred in 69% and 68% of subjects in the Coreg CR and Toprol XL groups, respectively. The most common AEs were peripheral edema, headache and fatigue. Non-fatal serious adverse events were reported during treatment for 4 subjects in the Toprol XL group and 8 subjects in the Coreg CR group. None of the serious adverse events were considered to be related to study medication by the Investigator. There were no deaths in the study.

On-therapy, n/N (%)	Toprol-XL N=278	Coreg CR N=290	Total N=568
Any AE	190/278 (68%)	200/290 (69%)	390/568 (69%)
Any Related AE	81/278 (29%)	89/290 (31%)	170/568 (30%)
Any AE by Maximum Intensity Mild	81/278 (29%)	88/290 (30%)	/568 (30%)
Moderate	85/278 (31%)	88/290 (30%)	/568 (30%)
Severe	18/278 (6%)	23/290 (8%)	41/568 (7%)
Any SAE	4/278 (1%)	8/290 (3%)	12/568 (2%)
Any AE Leading to Withdrawal of IP	19/278 (7%)	19/290 (7%)	38/568 (7%)

Most Frequently Reported On-therapy Adverse Events (those reported in>5% of either of the two treatment groups) (Safety Population: COR103561)

AE Preferred Term, n/N (%)	Toprol-XL N=278	Coreg CR N=290	Total N=568
Any Adverse Event	190 (68%)	200 (69%)	390 (69%)
Headache	33 (12%)	42 (14%)	75 (13%)
Edema peripheral	25 (9%)	29 (10%)	54 (10%)
Fatigue	29 (10%)	22 (8%)	51 (9%)
Dizziness	18 (6%)	28 (10%)	46 (8%)
Nasopharyngitis	17 (6%)	16 (6%)	33 (6%)
Upper respiratory tract infection	12 (4%)	19 (7%)	31 (5%)
Nausea	11 (4%)	18 (6%)	29 (5%)

Serious Adverse Events: There were no on-therapy or post treatment deaths reported during the study. An on-therapy SAE was defined as an SAE which occurred during the up-titration, maintenance, or down-titration phase, within 3 days post last dose. All on-therapy non-fatal SAEs are listed below. None of the serious adverse events were considered to be related to study medication by the Investigator.

Preferred Term	**Toprol XL (N=278)**	**Coreg CR (N=290)**
Any Event	4 (1%)	8 (3%)
Breast cancer	1 (<1%)	0
Chest discomfort	0	1 (<1%)
Colitis ischaemic	0	1 (<1%)
Depression suicidal	0	1 (<1%)
Gastrooesophageal reflux disease	0	1 (<1%)
Hydronephrosis	1 (<1%)	0
Hypertension	0	1 (<1%)
Myocardial infarction	0	1 (<1%)
Orthostatic hypotension	1 (<1%)	0
Palpitations	0	1 (<1%)
Peridiverticular abscess	1 (<1%)	0
Presyncope	1 (<1%)	0
Umbilical hernia	0	1 (<1%)

Conclusion: Coreg CR was superior to Toprol XL in with respect to effects on triglycerides in subjects with hypertension and normal lipids to mild dyslipidemia. There was no significant difference between the two treatment groups in HDL-C in this population. There were no significant differences between the two treatment groups in change from BL in BP or HR. Statistically significant decreases were observed in SBP and DBP from BL to MM6 within both treatment groups. The most common AEs were peripheral edema, headache and fatigue. Non-fatal serious adverse events were reported during treatment for 4 subjects in the Toprol XL group and 8 subjects in the Coreg CR group. None of the serious adverse events were considered to be related to study medication by the Investigator. There were no deaths in the study.

Publications: